REMARKS

Claims 1-47 are now pending in the application, of which Claims 23-26 and 37-44 are withdrawn, and Claims 1-22, 27-36 and 45-47 are rejected. Minor amendments have been made to the specification and claims to simply overcome the objections to the specification and rejections of the claims under 35 U.S.C. § 112. The amendments to the claims contained herein are intended to be of equivalent scope as originally filed and, thus, are not narrowing amendments. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

ELECTION PURSUANT TO RESTRICTION REQUIREMENT

Item 1. The Applicants thank the Examiner for considering the election with traverse of Group I. Applicants again request reconsideration of the requirement restricting Group I, Claims 1-22, 27-36 and 45-47, from Group II, Claims 23-26, for the following reasons. Original Claims 27-36 are directed to vaccines prepared by the method of Claim 23. Applicants believe that, even though these are distinct inventions, the vaccine product claims defined in original Claims 27-36 cannot be made by another materially different process other than that of original Claim 23. As a result, Applicants submit that, under MPEP 806.05(f), Group II is not susceptible to restriction from Group I. Applicants respectfully request rejoinder of Group II with Group I.

OBJECTION TO SPECIFICATION

Item 2. The Specification stands objected to for inadvertent misspellings of certain terms. Applicants have now reviewed and amended the Specification to correct occurrences of "Shiwanella" to "Shewanella", "Felixinobacter" to "Flexibacter", and "florescens" or "florescence" to "fluorescens". Applicants believe that these amendments overcome the objection, and respectfully request that it be withdrawn.

OBJECTIONS TO CLAIMS

Item 3. Claims 1-22, 27-36 and 45-47 stand objected to for reciting "AHMA." Applicants have now amended Claim 1 to recite "adhesin protein of Aeromonas hydrophila (AHMA)" to overcome this objection.

Item 4. Claims 1-22, 27-36 and 45-47 stand objected to for reciting "Shiwanella" and "Flexinobactor." Applicants have now amended Claims 22, 46 and 47 to recite "Shewanella" and "Flexibacter" respectively, and to correct "florescens" to "fluorescens".

Item 5. Claims 1-22, 27-36 and 45-47 stand objected to for reciting the term "FP." Applicants have now amended Claim 11 to recite "fusion protein from *Ichthyophthirius multifiliis* (FP)" to overcome this objection.

Item 6. Claims 1-22, 27-36 and 45-47 stand objected to for lack of underlining or italicization to indicate the names of the genus and species of organism(s) recited therein. Applicants have now amended Claims 22, 46 and 47 to italicize these binomials to overcome this objection.

Item 7. Claims 27-36 stand objected to for depending from a non-elected claim(s). Applicants have now inserted a new product claim 48 incorporating the features of the withdrawn Claim 23 and have amended Claims 27-36 to be dependent from the new product Claim 48.

Applicants believe that these amendments overcome the objections, and respectfully request that they be withdrawn.

REJECTION UNDER 35 U.S.C. § 112

Item 8. Claims 1-22, 27-36 and 45-47 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the Specification. The rejection alleges that the Specification does not reasonably provide enablement for *derivatives* of the recombinant protein major adhesin protein of *Aeromonas hydrophila* (AHMA).

This rejection is respectfully traversed. As indicated on pages 7 and 8 of the Specification, the cloning and expression of recombinant AHMA has been fully described in US Patent Application No. 10/220,986 to Sin et al. (the '986 application) entitled "Therapeutic and Prophylactic Agents Derived from

Aeromonas hydrophila bacterial surface proteins," published as US2004/0077067. The entire contents of the '986 application have been incorporated by reference in the present application.

The '986 application describes nucleotide and polypeptide sequences of a 43-kDa adhesin of *A. hydrophila* as well as **variants and derivatives of these sequences** (see for example, Para [0009]). Paras [0104] to [0158] describe polypeptide variants of the recombinant polypeptide, assay formats for detecting polypeptide variants, methods of producing polypeptide variants etc. Paras [0160] to [0174] of the '986 application describe polypeptide derivatives. Therefore it is respectfully submitted that the scope of the claims is commensurate with the enablement provided by the disclosure. It is also submitted that sufficient disclosure is provided in the Specification to allow one of skill in the art to make and use the invention *without undue experimentation*, relying on the patent specification and the knowledge in the art at the time the Specification was filed.

The terms "polypeptide variant" and "derivative" as defined in paras [0082] and [0065] respectively, of the '986 application are consistent with the Examiner's holding on protein stability (with reference to Creighton and Nosoh et al.).

Applying the Wands test factors for what constitutes "undue experimentation" to the present application (*In re Wands 8 USPQ2d 1400*), Applicants respectfully submit that:

1) In light of the disclosure in the present application and the '986 application, the necessary experimentation is not unduly extensive;

2) Sufficient direction or guidance is presented in the disclosures of the present application and that of the '986 application with respect to selecting other proteins having claimed functional features;

3) An adequate number of working examples are provided;

4) The relative skill of those in the art is commonly recognized as quite high (as acknowledged by the Examiner.

In light of the aforesaid, it is respectfully submitted that the Applicants have provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 9. Claims 5 and 12 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

Applicants respectfully disagree. However, solely to expedite the issuance of the present application, Applicants have now amended Claim 5 to recite "wherein the proportion of water and oil in the emulsion is in the ratio of 1:2." Support for the amendment may be found on page 11 of the Specification.

The Examiner has also applied this rejection to Claim 12. Applicants believe that this may be a typographical error, and have assumed that the rejection was intended to be applied to Claim 15 instead. As a result, Claim 15 has now been amended similarly to Claim 5. However, if Applicants'

understanding is incorrect, then Applicants request that this amendment to Claim 15 not be entered and that the Examiner provide further clarification as to the nature of the rejection of Claim 12 under 35 U.S.C. § 112, second paragraph.

Applicants believe that these remarks and amendments overcome the rejection and respectfully request that it be withdrawn.

Item 10. Claim 20 stands rejected under 35 U.S.C. § 112, second paragraph, for reciting the limitation "constituent proteins" on the grounds that there is allegedly insufficient antecedent basis for this limitation in the claim. Applicants have now amended Claim 20 to recite:

"The oral vaccine according to Claim 11 comprising immunologically effective dose of at least one of the proteins selected from the group consisting of recombinant protein AHMA, recombinant protein AHMA fragments, and recombinant protein derivatives."

Applicants believe that this amendment overcomes the rejection and respectfully request that it be withdrawn.

REJECTION UNDER 35 U.S.C. § 102

Item 11. Claims 1, 27-29 and 35-36 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Irianto et al. (*Journal of Fish Diseases*, February 2003, 26, 117-120). This rejection is respectfully traversed.

Irianto et al. discuss oral administration of formalin-inactivated **cells** of *Aeromonas hydrophila* A3-51 to treat *A. salmonicida* infection in goldfish. The oral vaccine composition in Irianto et al. comprises **dead cells** of A3-51 (see for example, page 118). Irianto et al. do not teach an oral vaccine composition

comprising *recombinant protein* AHMA. Therefore Irianto et al. do not disclose even a single limitation found in claim 1. A prior art reference anticipates a claim only if it discloses *each and every* limitation found in the claim. Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 12. Claims 1-3, 5-6, 10 and 27-29 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Fang et al. (*Journal of Fish Diseases*, 2000, 23, 137-145). This rejection is respectfully traversed.

Fang et al. disclose *intraperitoneal* immunization of blue gourami with the *Aeromonas hydrophila* major adhesin protein (a 43 kDa Outer Membrane Protein) in the presence of Freund's complete adjuvant (FCA). In animals, contact with Freund's complete adjuvant is reported as causing inflammation, induration, necrosis, hyperalgesia, chronic granulomas, ulcerations, abscesses, tissue sloughs, arthritis, neural or mechanical lameness, and peritonitis. As a result, ethical use of FCA in animals is generally limited to non-oral use in those situations where no more humane substitute adjuvant is available.

Claims 1-3, 5-6 and 10 are drawn to an **oral** vaccine comprising at least one of recombinant protein AHMA, recombinant protein AHMA fragments, and recombinant protein derivatives. Fang et al. do not disclose oral administration of the vaccine or even that the vaccine would be suitable for oral administration. In this regard, it should be noted that the route of delivering a vaccine is an important factor for successful immunization (see for example, page 3, 1st

sentence of the Specification) and can influence the strength of the resulting immune response.

Fang et al. do not address whether or not a vaccine composition containing proteins that exhibit immunogenicity when parenterally placed directly into, e.g., intramuscular, intravascular, or intraperitoneal, tissue can be administered orally to fish so as to retain significant immunogenicity. It is commonly understood that the vertebrate digestive system is effective to denature and hydrolyze many proteins. In this light, Fang et al. does not contain any teaching to provide AHMA proteins or their immunogenic fragments or derivatives in an orally administrable composition. Likewise, Fang et al. do not suggest oral administration of their FCA-containing composition. Instead, by choosing the very powerful FCA as the adjuvant in their parenteral vaccine composition, Fang et al. implicitly suggest that a powerful adjuvant may be required to achieve a significant immune response to AHMA proteins, even when they are administered parenterally. This in itself suggests that AHMA proteins may be only weakly immunogenic in vivo and, thus, that oral administration of AHMA proteins is unlikely to be an effective route for protective immunization against *Aeromonas hydrophila*.

More importantly, the recitation of the term "oral" in the preamble of the instant Claims is relevant to an understanding of the purpose and context of the invention – and is not merely a recitation of one use of a claimed composition -- when considered as a whole in light of the teachings of the Specification. The first recited object of the invention, as well as all the described embodiments of

the invention, state that the vaccine composition that has been invented is one for oral administration and that providing such an inventive orally administrable vaccine composition solves a number of problems in the field of fish immunization. As a result, in the present Claims, the preamble is necessary to give life, meaning, and vitality to the claimed subject matter.

Further, Fang et al. also do not disclose **recombinant** protein AHMA, **recombinant** protein AHMA fragments or **recombinant** protein derivatives. Instead Fang et al. disclose an AHMA protein that was isolated by using potassium thiocyanate.

Since Fang et al. do not disclose *each and every* limitation found in the Claim 1, it is respectfully submitted that Fang et al. do not anticipate Claims 1-3, 5-6, 10 and 27-29 under 35 U.S.C. §102(b). Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Item 13. Claims 1-3, 5-6, 10-13, 15-16, 20-21, 27-36 and 45 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wolf-Watz et al. (U.S. Pat. No. 5,284,653 published February 8, 1994) in view of Wang et al. (*Fish Shellfish Immunol.*, Nov. 2002;13(5):337-50). This rejection is respectfully traversed.

Wolf-Watz et al. disclose a fish vaccine comprising **live** avirulent, invasive and immunogenic strain of a fish pathogenic bacterial species such as *Aeromonas hydrophila*. Wang et al. disclose a vaccine composition comprising

the surface immobilization antigen of *Ichthyophthirius multifiliis* and Freund's complete adjuvant (FCA).

The rejected claims teach a vaccine composition comprising at least one of recombinant protein AHMA, or fragments or derivatives thereof, optionally in combination with another membrane protein (FP) and/or inactivated bacterial strains and/or inactivated viral strains.

Wolf-Watz et al. discuss the advantages of **live** vaccines over vaccines based on killed pathogens or bacterial components (see for example, column 2, lines 27-41). In view of these stated advantages, Wolf-Watz et al. teach administering live *A. hydrophila* optionally expressing additional antigenic determinants from other pathogens (see for example, column 6, lines 28-42). Wolf-Watz et al. thus ***teach away*** from the present claims which teach oral vaccine compositions based on bacterial component proteins optionally in combination with killed pathogens.

It would not be *prima facie* obvious to one of skill in the art to combine Wolf-Watz et al. with Wang et al. to arrive at the present claims, as the latter reference discloses a vaccine composition comprising a bacterial component (i-antigens), which the primary reference teaches *away from*.

Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 14. Claims 1-6, 10-16, 20-22, 27-36 and 45-47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wolf-Watz et al., Wang et al. as

set forth in Item 13 above, and further in view of Morinigo et al. (*Bulletin of the European Association of Fish Pathologists*, Nov. 2, 2002, Vol. 22, No. 5, pp. 298-303). This rejection is respectfully traversed.

Claims 22 and 46-47 are drawn to the oral vaccine of Claim 1 further comprising bacterial antigens of killed bacteria selected from the group consisting of bacterial antigens or killed bacteria selected from the group consisting of *Shewanella putrefaciens, Pseudomonas fluorescens, Vibrio alginolyticus* and *Flexibacter columnaris*.

The teachings of Wolf-Watz et al. and Wang et al. are described above. Morinigo et al. discuss a divalent vaccine composition comprising formalized (inactivated) whole cells and extracellular products (ECPs) of virulent strains of *Vibrio alginolyticus* and *Photobacterium damselae*.

As discussed above, Wolf-Watz et al. ***teach away*** from the present claims as Wolf-Watz et al. discuss the advantages of **live** vaccines over vaccines based on killed pathogens or bacterial components. Therefore, it would not be *prima facie* obvious to combine Wolf-Watz et al. with Wang et al. for reasons also discussed above.

For the same reason, it would also not be *prima facie* obvious at the time the invention was made to add the *V. alginolyticus* and *P. damselae* antigens as taught by Morinigo et al to the vaccine composition of Wolf-Watz et al.

Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 15. Claims 1-6, 10-16, 20-22, 27-36 and 45-47 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Wolf-Watz et al., Wang et al. and Morinigo et al. as set forth in Items 13 and 14 above, and further in view of Chen et al. (U.S. Patent No. 6,720,001 B1, published April 13, 2004). This rejection is respectfully traversed.

Claims 4 and 14 are drawn to the oral vaccine of Claim 1 further comprising palm oil. As discussed in Items 13 and 14 above, it would not be *prima facie* obvious to combine Wolf-Watz et al., Wang et al. and Morinigo et al.

Chen et al. disclose pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredients. Chen et al. teach that the oil component of the oil-in-water emulsion may not be appropriately polar to effectively incorporate polyfunctional active ingredients at desirable therapeutic levels, without compromising product safety (see, for example, column 2, lines 7-12). In order to overcome this problem, Chen et al. disclose oil-in-water emulsions "wherein the oil phase includes components chosen to increase the polarity of the oil phase"... etc. (see column 3, lines 55-62).

Thus, even if Wolf-Watz et al., Wang et al. and Morinigo et al. could be combined, it would not be *prima facie* obvious to add just the palm oil as taught by Chen et al. in view of the disadvantage discussed in the preceding paragraph.

Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

Item 16. Claims 1-22, 27-36 and 45-47 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Wolf-Watz et al., Wang et al., Morinigo et al. and Chen et al. as set forth in Item 15 above, and further in view of Calanchi et al. (U.S. Patent No. 5,008,117, published April 16, 1991). This rejection is respectfully traversed.

Claims 7-9 and 17-19 are drawn to the oral vaccine of Claim 2 further mixed with a binding agent.

Calanchi et al. teach a method of dispersing thickening agents in pharmaceutical formulations for effective delivery of micro-encapsulated drugs, which otherwise have the tendency to precipitate or float.

As discussed in Items 13, 14 and 15 above, it would not be *prima facie* obvious to combine Wolf-Watz et al., Wang et al., Morinigo et al. and Chen et al. Therefore, it would also not be *prima facie* obvious to add carboxymethylcellulose as taught by Calanchi et al. at the time the invention was made to the vaccine composition of Wolf-Watz et al, Wang et al, Morinigo et al and Chen et al.

Applicants believe that these remarks overcome the rejection and respectfully request that it be withdrawn.

CONCLUSION

Applicants wish to thank the Examiner for accepting the drawings as filed. It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully

request that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600. Favorable reconsideration and allowance of the Application is requested in light of the newly amended claims and accompanying remarks.

Respectfully submitted,

Dated: 3/17/05

By: _____

Paul A. Keller, Reg. No. 29,752
Mark S. Scott, Reg. No. 43,101

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

PAK:MSS:mhe